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<p>Previous research has shown that the acoustic startle response, a simple reflex mediated by four synapses in the brainstem and spinal cord, can be increased when elicited in the presence of a stimulus previously paired with a footshock. This "fear-potentiated startle effect" can be selectively blocked by drugs that decrease anxiety in humans as well as by lesions of the central nucleus of the amygdala, an area of the brain known to be critical for fear. This year it has been found that a) footshocks by themselves cause a marked increase in the startle reflex which appears to result from an activation of the central nucleus of the amygdala; b) low level electrical stimulation of the central nucleus of the amygdala increases the acoustic startle reflex with a transit time of about 5 msec from the amygdala to the acoustic startle circuit; c) a direct anatomical connection exists between the central nucleus of the amygdala and the acoustic startle pathway and d) lesions at several points along this pathway prevent a fear stimulus from potentiating the startle reflex.</p>			
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AFOSR - PROGRESS REPORT

MICHAEL DAVIS - YALE UNIVERSITY

JULY 1, 1987 - JUNE 30, 1988

Research objectives

Previous research has shown that the acoustic startle response, a simple reflex mediated by four synapses in the brainstem and spinal cord, can be increased when elicited in the presence of a stimulus previously paired with a footshock. This "fear-potentiated startle effect" can be selectively blocked by drugs that decrease anxiety in humans as well as by lesions of the central nucleus of the amygdala, an area of the brain known to be critical for conditioned fear. A major goal of the work supported by the AFOSR is to determine the site of plasticity in the brain that mediates fear conditioning. Experiments this last year have focussed on the question of a) defining the unconditioned response in the fear-potentiated startle test and b) whether there is a direct anatomical connection between the central nucleus of the amygdala and the acoustic startle pathway and, if so, whether surgical interruption of this pathway prevents a fear stimulus from increasing startle.

Accomplishments and progress

The following findings have been obtained: a) footshocks by themselves cause a delayed but marked increase in the startle reflex elicited by an auditory stimulus, a phenomenon termed "shock sensitization of startle"; b) this effect is completely blocked by lesions of the central nucleus of the amygdala but not by lesions of the immediately adjacent lateral nucleus; c) shock sensitization appears to alter acoustic startle by affecting neural transmission at the same point along the acoustic startle pathway where conditioned fear alters transmission; d) using the sensitive Phaseolus vulgaris-leucoagglutinin anterograde tracing technique a strong and direct projection has been found between the central nucleus of the amygdala and the exact part of the reticular formation known to be critical for acoustic startle; e) lesions at several different points along this pathway eliminate fear-potentiated startle as well as shock-sensitization and f) single pulse electrical stimulation of the central nucleus of the amygdala increases acoustic startle with a transit time from the amygdala to the startle pathway of about 5 msec, consistent with a direct, perhaps monosynaptic connection.

Working conclusions and future studies

Based on these results it is hypothesized that an unconditioned stimulus such as footshock or a conditioned stimulus paired with footshock increases the acoustic startle reflex by activation of the central nucleus of the amygdala. Activation of the amygdala then increases startle via a direct, perhaps monosynaptic, connection between the central nucleus of the amygdala and the nucleus reticularis pontis caudalis, an obligatory part of the startle pathway. Because we have found that local infusion into the amygdala of specific peptides such as thyrotropin releasing hormone increases startle, it

is possible that footshock and/or a conditioned stimulus activates the amygdala by releasing a peptide, which are highly concentrated in the amygdala. Moreover, because both conditioned and unconditioned stimuli appear to activate the amygdala, it is possible that the amygdala represents the actual site of plasticity which mediates long-term memory of a fear stimulus.

To test these hypotheses, procedures are being developed to allow reversible inactivation of the amygdala to determine whether a) cooling the amygdala during fear conditioning (i.e., during the actual pairings of a light and a shock) will block the acquisition of fear conditioning; and b) whether local infusion of excitatory amino acid antagonists into the amygdala, which could prevent the input of stimulus information, will block the acquisition of fear conditioning. To evaluate the role of peptides, startle will c) be tested after local infusion into the amygdala of various peptides implicated in fear from other work (e.g., thyrotropin releasing hormone, calcitonin gene related peptide, corticotropin releasing factor). It will also be determined whether d) pairing direct activation of the amygdala (either by electrical stimulation or by infusion of peptides) with a neutral stimulus will produce fear-potentiated startle; and (eventually) whether e) local infusion of peptide antagonists or antibodies in the amygdala will block shock sensitization as well as acquisition of fear-conditioning.

Articles accepted for publication based on this work:

Davis, M. Sensitization of the acoustic startle reflex by footshock.
Behavioral Neuroscience

Hitchcock, J.M., Sananes, C.B. and Davis, M. Sensitization of the startle reflex by footshock: Blockade by lesions of the central but not the lateral nucleus of the amygdala. Behavioral Neuroscience

Boulis, N.M. and Davis, M. Footshock induced sensitization of electrically elicited startle reflexes. Behavioral Neuroscience

Rosen, J.B. and Davis, M. Temporal characteristics of enhancement of startle by stimulation of the amygdala. Physiology and Behavior

Articles submitted for publication based on this work:

Davis, M., Schlesinger, L.S. and Sorenson, C.A. Temporal specificity of fear conditioning: Effects of different CS-US intervals on the fear-potentiated startle effect

Articles planned for submission during the coming year:

Hitchcock, J.M. and Davis, M. Efferent pathways of the amygdala involved in conditioned fear as measured with the fear-potentiated startle paradigm.

Rosen, J.B., Hitchcock, J.M., Sananes, C.B., Miserendino, M and Davis, M. A direct pathway from the central nucleus of the amygdala to the region of the nucleus reticularis pontis caudalis critical for startle.

Professional personnel

Janice Hitchcock Ph.D. received June, 1988. The role of afferent and efferent pathways of the amygdala in fear-potentiated startle.

Jeff Rosen Ph.D. Postdoctoral fellow

Catherine Sananes Ph.D. Postdoctoral fellow

Mindy Miserendino Ph.D. Postdoctoral fellow

Serge Campeau Graduate Student

Kate Melia Graduate Student

Ken Liang Visiting Professor

Papers delivered relevant to this work:

Neurosubstrates of fear and anxiety: The role of the amygdala. Invited symposium speaker, The Royal Society, British Society of Pharmacology, London England, Oct. 30, 1987

A neural systems approach to fear and anxiety (Chairman). A symposium at the Society for Neuroscience, New Orleans, LA., Nov. 17, 1987.

Fear-potentiated startle as a model system for analyzing learning and memory. Air Force Office of Scientific Research, Review of Air Force sponsored basic research in neuroscience, San Antonio, Texas, Nov. 30, 1987.

Fear potentiated startle in relationship to other models of fear conditioning. Invited symposium participant, Twelfth Annual Winter Conference on The Neurobiology of Learning and Memory, Park City, Utah, Jan. 9, 1988.

Neural mechanisms of fear conditioning. Neuroscience Retreat, Feb. 20, 1988.